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International Bureau(43) International Publication Date  
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PCT

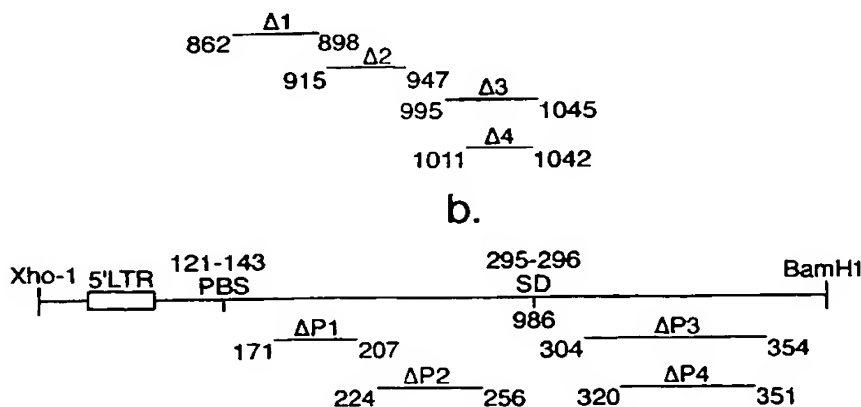
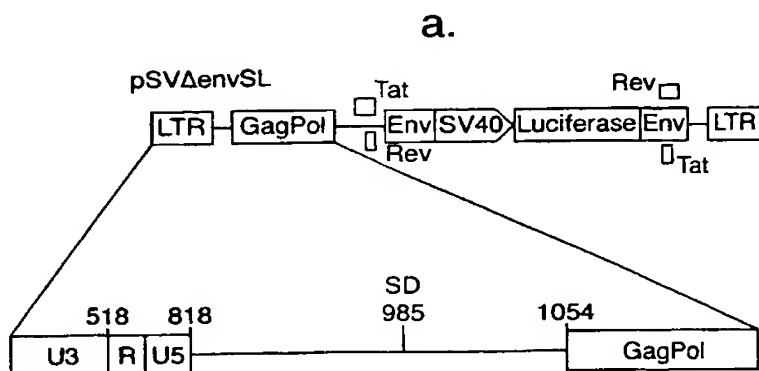
(10) International Publication Number  
**WO 00/75351 A1**(51) International Patent Classification<sup>7</sup>: **C12N 15/86**,  
7/00, A61K 48/00, C12N 15/11(21) International Application Number: **PCT/GB00/02263**(22) International Filing Date: **9 June 2000 (09.06.2000)**(25) Filing Language: **English**(26) Publication Language: **English**(30) Priority Data:  
9913459.5 9 June 1999 (09.06.1999) **GB**  
9916911.2 19 July 1999 (19.07.1999) **GB**(71) Applicant (for all designated States except US): **SYNGENIX LIMITED** [GB/GB]; Home Farm, Fowlmere Road, Heydon Near Royston, Herts SG8 8PG (GB).

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(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,

[Continued on next page]

(54) Title: **SIV-BASED PACKAGING-DEFICIENT VECTORS**

(57) Abstract: A simian Immunodeficiency Virus (SIV) genome having a mutation within the packaging signal such that viral RNA is not packaged within an SIV capsid is described. A viral vector comprises an SIV packaging signal and a heterologous gene capable of being expressed in the vector. The packaging defective SIV genome and viral vector may be co-transfected into a host cell to produce SIV virus particles capable of expressing a heterologous gene.



ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

**Published:**

— With international search report.

(84) **Designated States (regional):** ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>N.79496B GCW</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/GB 00/ 02263</b>	International filing date (day/month/year) <b>09/06/2000</b>	(Earliest) Priority Date (day/month/year) <b>09/06/1999</b>
Applicant  <b>SYNGENIX LIMITED</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

### 1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☒ contained in the international application in written form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

**SIV-BASED PACKAGING-DEFICIENT VECTORS**

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☒ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

1

☐ None of the figures.

## INTERNATIONAL SEARCH REPORT

International Application No.

GB 00/02263

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/86 C12N7/00 A61K48/00 C12N15/11

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HARRISON GEOFFREY P ET AL: "Functional analysis of the core human immunodeficiency virus type 1 packaging signal in a permissive cell line." JOURNAL OF VIROLOGY, vol. 72, no. 7, July 1998 (1998-07), pages 5886-5896, XP002147391 ISSN: 0022-538X	1-6, 14-16, 19
Y	the whole document --- -/--	7-13, 17, 18



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&amp;" document member of the same patent family

Date of the actual completion of the international search

14 September 2000

Date of mailing of the international search report

29/09/2000

Name and mailing address of the ISA

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Authorized officer

Smalt, R

## INTERNATIONAL SEARCH REPORT

International Application No

P 00/02263

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	MCBRIDE M SCOTT ET AL: "The human immunodeficiency virus type 1 encapsidation site is a multipartite RNA element composed of functional hairpin structures." JOURNAL OF VIROLOGY, vol. 70, no. 5, 1996, pages 2963-2973, XP002147392 ISSN: 0022-538X	1-6, 14-16, 19
Y	the whole document	7-13, 17, 18
X	BERKHOUT BEN ET AL: "Role of the DIS hairpin in replication of human immunodeficiency virus type 1." JOURNAL OF VIROLOGY, vol. 70, no. 10, 1996, pages 6723-6732, XP002147393 ISSN: 0022-538X	1-6, 14-16, 19
Y	the whole document	7-13, 17, 18
X	MCCANN E M ET AL: "LOCATION OF CIS-ACTING SIGNALS IMPORTANT FOR RNA ENCAPSIDATION IN THE LEADER SEQUENCE OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 2" JOURNAL OF VIROLOGY, US, THE AMERICAN SOCIETY FOR MICROBIOLOGY, vol. 71, no. 5, 1997, pages 4133-4137, XP000909426 ISSN: 0022-538X	1, 2, 4-6, 14-16, 19
Y	page 4135, left-hand column, paragraph 2 -page 4136, left-hand column, paragraph 1	7-13, 17, 18
Y	WO 97 48277 A (GAGE FRED H ; SUHR STEVEN T (US); SALK INST FOR BIOLOGICAL STUDI (U) 24 December 1997 (1997-12-24) see whole document, particularly page 6, 2-3. the whole document	7-13, 17, 18
A	WO 99 04026 A (CHIRON CORP) 28 January 1999 (1999-01-28) see whole document, particularly page 2, lines 22-24, page 6, lines 15-28, and claim 9.	7-13, 17, 18

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## INTERNATIONAL SEARCH REPORT

International Application No

P GB 00/02263

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>RIZVI TAHIR A ET AL: "Simian immunodeficiency virus RNA is efficiently encapsidated by human immunodeficiency virus type 1 particles." JOURNAL OF VIROLOGY, vol. 67, no. 5, 1993, pages 2681-2688, XP000946026 ISSN: 0022-538X cited in the application the whole document</p> <p>---</p>	
T	<p>LEVER A M L ET AL: "GENE THERAPY: FROM BENCH TO BEDSIDE. LENTIVIRUS VECTORS FOR GENE THERAPY" BIOCHEMICAL SOCIETY TRANSACTIONS, GB, COLCHESTER, ESSEX, vol. 27, no. 6, December 1999 (1999-12), pages 841-847, XP000915750 ISSN: 0300-5127 the whole document</p> <p>-----</p>	

# INTERNATIONAL SEARCH REPORT

Information on patent family members

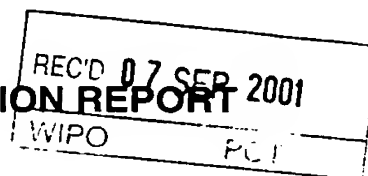
International Application No

GB 00/02263

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9748277	A	24-12-1997	AU	3212197 A	07-01-1998
WO 9904026	A	28-01-1999	AU	8576298 A	10-02-1999
			EP	1003894 A	31-05-2000

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)





Applicant's or agent's file reference N.79496B GCW		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB00/02263	International filing date (day/month/year) 09/06/2000	Priority date (day/month/year) 09/06/1999
International Patent Classification (IPC) or national classification and IPC C12N15/86		
Applicant SYNGENIX LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.  
  
☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand  19/12/2000	Date of completion of this report  03.09.2001
Name and mailing address of the international preliminary examining authority:   European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523655 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Friedrich, C  Telephone No. +49 89 2399 7721  



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB00/02263

**I. Basis of the report**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, pages:**

1-28 as originally filed

**Claims, No.:**

1-19 as originally filed

**Drawings, sheets:**

1/7-7/7 as originally filed

**Sequence listing part of the description, pages:**

1-3, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB00/02263

- ☐ the description,      pages:  
☐ the claims,      Nos.:  
☐ the drawings,      sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.  
☒ claims Nos. 17-18.

because:

- ☒ the said international application, or the said claims Nos. 17-18 relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.  
☐ the computer readable form has not been furnished or does not comply with the standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02263

## 1. Statement

Novelty (N)	Yes:	Claims	1-6, 11-19
	No:	Claims	7-10
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-6, 11-19
Industrial applicability (IA)	Yes:	Claims	1-16, 19
	No:	Claims	

## 2. Citations and explanations **see separate sheet**

## VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:  
**see separate sheet**

Reference is made to the following documents:

- D1: Rizvi, TA et al., 1993. Simian immunodeficiency virus RNA is efficiently encapsidated by human immunodeficiency virus type 1 particles. JOURNAL OF VIROLOGY 67:2681-2688.
- D2: Rud, EW et al., 1994. Molecular and biological characterization of simian immunodeficiency virus macaque strain 32H proviral clones containing nef size variants. J Gen Virol 75:529-43. (cited by the applicant)
- D3: Naldini, L et al., 1996. In vivo gene delivery and stable transduction of non-dividing cells by a lentiviral vector. Science 272:263-267. (The document was not cited in the international search report. A copy is appended hereto.)
- D4: Berkhout, B et al., 1996. Role of the DIS hairpin in replication of human immunodeficiency virus type 1. JOURNAL OF VIROLOGY 70: 6723-6732.
- D5: McCann EM et al., 1997. Location of cis-acting signals important for RNA encapsidation in the leader sequence of human immunodeficiency virus type 2. JOURNAL OF VIROLOGY 71:4133-4137.

### **Introduction**

The present application refers to packaging deficient SIV viruses (claims 1-6), the generation and use of viral vectors comprising an SIV packaging sequence (claims 7-13, and 17), and sense or antisense packaging sequences from SIV for treatment or prophylaxis of SIV or HIV infection (claims 14-16, and 18-19). Since vectors comprising an SIV packaging sequence and gene delivery systems based on other lentiviruses are part of the prior art, objections are raised concerning novelty (claims 7-10) and inventive step (claims 1-6 and 11-19). No opinion regarding industrial applicability is formulated concerning subject-matter related to the treatment of the human or animal body (claims 17-18).

### **Re Item III**

#### **Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claims 17-18 relate to subject-matter considered by this authority to be covered by the provisions of Rule 67.1(iv), PCT (the treatment of the human or animal body).

Consequently, no opinion will be formulated with regard to industrial applicability concerning subject-matter of these claims according to Art.34(4)(a)(i), PCT.

**Re Item V**

**Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Novelty, Art.33(1) and (2), PCT**

1.1 Claims 7-10 concern vectors comprising an SIV packaging signal and a heterologous gene expressed by said vector. D1 discloses such vectors, namely pTR150 and 170, which comprise an SIV leader sequence and a heterologous gene (Hyg<sup>R</sup>). Therefore subject-matter of claims 7-10 is not new according to Art.33(1) and (2), PCT.

**2. Inventive Step, Art.33(1) and (3), PCT**

2.1. Claims 1-6 concern packaging deficient SIV genomes with mutations or deletions between the PBS and the gag initiation codon. D2, which discloses the sequence of a wild-type SIV genome, may be considered the closest prior art and the provision of a packaging deficient SIV genome the technical problem. It is known from prior art that packaging sequences of the related HIV-1 and -2 are located between the PBS and the gag initiation codon (see Fig.1 in D4, abstract of D5 and the description of the present application on page 23, lines 9-14). D1 provides strong evidence that also in SIV the analogous sequence is important for encapsidation (see Fig.2 and Table 1). Although one cannot predict the exact site or size of the SIV packaging signal, it requires not more than standard technical procedures known to the skilled person in the art to achieve a solution to the present problem by simply generating deletion mutants and test them for packaging efficiency, as has been done previously for HIV. Thus subject-matter of claims 1-6 is not considered inventive in the sense of Art.33(3), PCT.

2.2. Claims 11-13 and 17 concern the generation of an SIV virus encoding a heterologous gene and a pharmaceutical composition comprising said virus. D3 discloses a process of generating an HIV virus encoding either luciferase or  $\beta$ -galactosidase, comprising the use of a packaging deficient HIV construct and a construct comprising the 5' leader of HIV (see figure 1 in D3). In the light of the closest prior art the technical problem is considered the provision of a vector system analogous

to the HIV-system disclosed in D3, based on the genome sequence of SIV. Regarding the lack of novelty or inventive step of the subject-matter of claims 1-10, the solution to this problem is a mere substitution of the components of the HIV vector system with those of the related SIV without the generation of surprising effects. Thus subject-matter of claims 11-13, and 17 is not considered inventive in the sense of Art.33(3), PCT.

2.3. Claims 14-16 and 18-19 concern the treatment or prophylaxis of SIV or HIV with a sense or antisense packaging sequence of SIV. The treatment of cells with sense or antisense sequences to compete with or abolish the function of essential nucleic acid sequences is considered well known in the art at the time of the present application. To apply said methodology on SIV or HIV packaging sequences may be considered the technical problem. The solution of said problem is not more than a straightforward extrapolation from the prior art to SIV or HIV sequences of predictable function, which will not elicit unexpected effects. Thus subject-matter of claims 14-16 and 18-19 is not considered inventive in the sense of Art.33(3), PCT.

### **Re Item VIII**

#### **Certain observations on the international application**

##### **1. Clarity of Claims and Support by the Description, Art.6, PCT**

1.1. Claim 1 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claim attempts to define the subject-matter in terms of the result to be achieved which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result should be added (see also PCT Guidelines, III-4.7).

1.2. Claims 7 and 14 refer to an SIV packaging sequence without providing technical features defining said sequence. Thus said claims are not clear according to Art.6 and Rule 6.3(b), PCT (see also PCT Guidelines, III-4.4).

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## P ENT COOPERATION TREA

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner  
 US Department of Commerce  
 United States Patent and Trademark  
 Office, PCT  
 2011 South Clark Place Room  
 CP2/5C24  
 Arlington, VA 22202  
 ETATS-UNIS D'AMERIQUE  
 in its capacity as elected Office

<b>Date of mailing</b> (day/month/year) 09 February 2001 (09.02.01)	
<b>International application No.</b> PCT/GB00/02263	<b>Applicant's or agent's file reference</b> N.79496B GCW
<b>International filing date</b> (day/month/year) 09 June 2000 (09.06.00)	<b>Priority date</b> (day/month/year) 09 June 1999 (09.06.99)
<b>Applicant</b> LEVER, Andrew et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:  
 19 December 2000 (19.12.00)

☐ in a notice effecting later election filed with the International Bureau on:  
 \_\_\_\_\_

2. The election ☒ was  
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

<b>The International Bureau of WIPO</b> 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Olivia TEFY Telephone No.: (41-22) 338.83.38
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